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| 09/944,493 | 08/22/2001 | Susan Wembach | ISIS-4823 | 9925 |

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| EXAMINER | |
|---|---|
| ZARA, JANE I | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1635 | 10 |

DATE MAILED: 10/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 09/944,493 | Weinbach et al |
| **Examiner** | **Art Unit** |
| Jane Zara | 1635 |

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) X Responsive to communication(s) filed on *Jul 18, 2003* .

2a) This action is **FINAL**. 2b) X This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4) X Claim(s) *1 and 3-23* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) X Claim(s) *1 and 3-23* is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some* c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____ .
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) X Notice of References Cited (PTO-892)
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) Information Disclosure Statement(s) (PTO-1449) Paper No(s).
4) Interview Summary (PTO-413) Paper No(s).
5) Notice of Informal Patent Application (PTO-152)
6) Other:

## DETAILED ACTION

This Office action is in response to the communication filed July 18, 2003, paper No. 9.

Claims 1, 3-23 are pending in the instant application.

### *Response to Arguments and Amendments*

Any rejection not repeated in this Office action is hereby withdrawn.

Applicant's arguments with respect to claims 1, 3-20 have been considered but are moot in view of the new ground(s) of rejection.

*New Rejections*

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor

and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 3-23 are rejected under 35 U.S.C. 103(a) as being unpatentable and Chen et al (USPN 6,458,383), the combination in view of Chen et al (USPN 5,508,040) and Bai, and further in view of Friedman et al, Cochrum et al, Robinson et al and Baracchini et al.

The claims are drawn to compositions and methods of enhancing the absorption of an antisense oligonucleotide, including a steroid anti-inflammatory, in a mammal, including humans, comprising the administration of an oral formulation comprising a first population of cationic particles comprising an antisense oligonucleotide and a penetration enhancer which are released at a first location in the intestine, and which penetration enhancer is optionally a chelator, fatty acid or bile salt, or comprises a poly-L lysine and alginate, and which penetration enhancer optionally comprises a bioadhesive, and a second population of particles comprising a penetration enhancer and a delayed release coating or matrix, and which second population is the same or different composition of the first, and optionally comprises polyethylene glycol, and is released at a location in the intestine that is downstream from the first location, and which antisense oligonucleotide comprises 2'-methoxyethoxy sugar moieties.

Chen et al (USPN 6,458,383) teach compositions and methods of enhancing the absorption of a drug in a mammal, including humans, comprising the administration of an oral formulation comprising a population of cationic particles comprising an oligonucleotide and a

penetration enhancer which are released at a first location in the intestine, and which penetration enhancer comprises a fatty acid (caprylic, lauric, capric), a bile acid (cholic, deoxycholic), a chelating agent (EDTA, citrate, salicylate), and another population of particles comprising a penetration enhancer and a delayed release coating or matrix, and polyethylene glycol, which second population is the same or different composition of the first, and is released at a location in the intestine that is downstream from the first location (See entire document, especially col. 7-8, 9-15, 19-23, 28-32, claims 1, 18, 24, 56, 70, 71, 91).

Chen et al (USPN 6,458,383) do not teach the administration of antisense oligonucleotides, nor oligonucleotides comprising 2'-methoxyethoxy sugar moieties, within delayed release carrier particles, a first and a second population of particles or optionally comprising a bioadhesive agent, the delayed release particles comprising poly-L-lysine and alginate, nor optionally comprising a steroid anti-inflammatory agent.

Chen (USPN 5,508,040) teaches a first and second population of particles, which second population of particles comprises penetration enhancers that are released at a time later in the intestinal tract (abstract; figures 1-3; col. 3, line 36-col. 4, line 16; col. 5, lines 10-38; claims 1, 16 and 18).

Bai teaches a first and second population of particles, which second population of particles comprises penetration enhancers that are released at a time later in the intestinal tract (see col. 1, line 36-col. 3, line 43; claim 1).

Friedmen et al teach particles for delayed release of biological substances comprising antisense oligonucleotides and further comprising alginate (See especially col. 43-45 and col. 47).

Cochrum et al teach particles for controlled or delayed release of biological substances in an organism, which particles comprise poly-L-lysine and alginate (See especially col. 6, lines 53-55; col. 8, line 49-col. 9, line 17).

Robinson et al teach carrier particles for delayed release of biological substances, which particles comprise bioadhesive agents and further comprise a steroid anti-inflammatory agent (See e.g. page 6, lines 14-18; page 11, line 24-page 13, line 13).

Baracchini et al teach the incorporation of 2'-methoxyethoxy sugar moieties into antisense oligonucleotides for enhancing their stability (col. Col. 2, line 58- col. 3, line 14).

It would have been obvious to one of ordinary skill in the art to utilize compositions (for delayed release of a drug) comprising a first population of particles comprising a drug and a penetration enhancer which are released at a first location in the intestine, and which particles comprise a bioadhesive, and a second population of particles comprising a penetration enhancer and a delayed release coating or matrix, which second population is the same or different composition of the first, and is released at a location in the intestine that is downstream from the first location, because Chen et al (USPN 6,458,383), Chen et al (USPN 5,508,040) and Bai teach first and second populations of particles for delayed drug release in a mammal including humans. One or ordinary skill in the art would have been motivated to compose and utilize particles containing bioadhesives, because Robinson et al teach the incorporation of bioadhesives into

delayed release particles in order to adhere to the area (e.g. of the digestive tract) that is contacted, release the biological agent or drug at a controlled rate and cause treating agent to be sorbed in the vicinity of the contacted area (See esp. Page 7, line 29-page 8, line 7 of Robinson). It would have been obvious to one of ordinary skill in the art to utilize compositions (for delayed release of a drug) comprising a first population of particles comprising a drug and a penetration enhancer which are released at a first location in the intestine, and which penetration enhancer comprises poly-L-lysine and alginate, and a second population of particles comprising a penetration enhancer and a delayed release coating or matrix, and polyethylene glycol, which second population is the same or different composition of the first, and is released at a location in the intestine that is downstream from the first location, because Chen et al (USPN 5,508,040) and Bai teach first and second populations of particles for delayed drug release in a mammal including humans, and which Friedmen et al teaches drugs or biological agents within these particles to include oligonucleotides. Friedman et al teach particles for delayed release, which particles comprise antisense oligonucleotides and alginate, and Cochrum et al teach particles for delayed release of biological substances in an organism including humans comprising poly-L lysine and alginate. One of ordinary skill in the art would have been motivated to use slow release particles for enhanced delivery of antisense oligonucleotides within the digestive tract and that the delivery of antisense oligonucleotides to the digestive tract would be enhanced using delayed release particles described by either Chen et al, Friedman et al or Cochrum et al. Furthermore, one of ordinary skill would have expected that poly-L lysine and alginate provide appropriate particle

constituents for delayed release of antisense oligonucleotides because Cochrum et al teach compositions for delayed release of biological active substances (including DNA and RNA), comprising slow release particles which comprise alginate and poly-L lysine, and which particles provide more complete and uniform coating of biological agents. One of ordinary skill in the art would have been motivated to administer steroid anti-inflammatory agents using these slow release particles for treatment of conditions related to inflammation, as taught previously by Robinson. One of ordinary skill in the art would have expected that these delayed release particles comprising a bioadhesive (and for delivery of an anti-inflammatory agent) are biocompatible with the gastrointestinal tract and furthermore that the incorporation of bioadhesives facilitates in the desired and slow release of biological agents at desired portions of the digestive tract. One of ordinary skill in the art would have been motivated to incorporate 2'-methoxyethoxy sugar moieties into antisense oligonucleotides for enhancing their stability and one would have expected that antisense comprising these modifications would be less susceptible to nuclease degradation.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

***Allowable Subject Matter***

No claims are allowed.

***Conclusion***

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

*JZ*

October 5, 2003

RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER